REMARKS

Applicants request entry of the amendment, reconsideration of the application, and timely notice of allowability. Claims 26-64 are now pending and are being examined.

The amendments to claims 26, 29, 30, 40, 43, 47, and 48 reflect a clarification in the terminology used for the "first recombinant DNA" of the claims. As clearly pointed out in the specification at page 33, lines 13-14, and at page 10, lines 11-25, the "therapeutic" gene of the invention can encompass bacterial genes and marker genes such as the LacZ gene. To clarify this specifically disclosed and exemplified embodiment, applicants have changed the term "therapeutic" gene in the claims to a "first" gene or simply "the" gene. This change more accurately reflects the nature of one aspect of the invention, where bacterial genes such as LacZ can be used to determine and monitor the successful expression from the recombinant adenovirus. This amendment is not made for reasons related to the patentability of the claims and applicants relinquish no subject matter by making this amendment. No new matter enters by these amendments.

New claims 57-60 are directed to specific genes that can be incorporated into the recombinant adenovirus of the claims. These genes are specifically disclosed at page 11, line 19, through page 12, line 4 of the specification. Thus, no new matter enters by these claims.

New claims 61-64 find support in the specification as a whole and, more particularly, Example 2 at pages 38-43 of the specification. The data presented in Table III at page 42 clearly indicates that cells expressing the gene of interest (LacZ) express the gene much longer when the compositions and methods of the invention are used. No new matter enters by these claims.

Furthermore, the new claims, as well as all the pending claims, are enabled by the specification. The discussion below points to articles in the scientific literature, such as the Poller *et al.* article (copy enclosed with a form PTO 1449), where methods and compositions encompassing the specifically recited factor IX gene have been used successfully in a recombinant adenovirus as the specification discloses. The factor IX gene was expressed in an adenoviral system and the use of an immunoprotective gene and an immunosuppressive agent, as recited in the claims, prolonged expression of factor IX. This independent confirmation of the teachings and examples shown in the specification buttresses applicants' statements in their enabling disclosure. In light of this additional evidence, applicants respectfully request allowance of all the pending claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Only one rejection remains in the case. Claims 26-56 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to provide an enabling disclosure for a composition comprising any immunosuppressive agent and a recombinant adenovirus containing a therapeutic gene and any immunoprotective gene.

Applicants respectfully disagree.

An applicant need not show that every possible embodiment that falls under the claims actually works in order to show that the claims are enabled. A reasonable understanding of one skilled in the art and the logical extensions from the data provided in the specification can make a single working example, or even no working example, suffice. In re Borkowski, 164 U.S.P.Q. 642, 645-6 (C.C.P.A. 1970).

It is also inappropriate to consider the scope of applicant's enabling disclosure as limited to only the exemplified embodiments. The examples add to understanding one skilled in the art would glean from the disclosure rather than limit the meaning or scope of the concepts therein. In re Koller, 204 U.S.P.Q. 702, 705-6 (C.C.P.A. 1980). Furthermore, if one skilled in the art can easily determine what the inoperative embodiments are, a claim need not specifically exclude the inoperative embodiments in order to be enabled. W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983).

As will be shown in detail below, there is no reason to doubt the statements in the specification that support the enablement of all the currently pending claims. The focus, in Paper No. 13, on what the examples do not show rather than on what they do show has inadvertently shifted attention away from the fact that methods and compositions as taught and claimed have been made and used by the inventors and others in the art.

Initially, however, applicants point out the synergistic effect of applicants' invention. At page 8 of the specification, lines 6-12, applicants state that at least an aspect of the invention "ensues from the demonstration of a particularly substantial synergistic effect, which is associated with the combined use of a recombinant adenovirus, in which expression of a gene of therapeutic importance is coupled to that of an immunoprotective gene, such as previously described, and of at least one immunoprotective agent." It is not, therefore, only a particular combination of immunosuppressive agent with a particular immunoprotective gene that makes the invention work. Rather, the combined application of elements creates expression levels that persist for extended time periods. To one of skill in the art, applicants have clearly demonstrated this in their specification.

With respect to the PTO's comments in Paper No. 13, one skilled in the art would not consider the selection of an immunosuppressive agent an arduous or unpredictable task. Many immunosuppressive agents are known and routinely used to suppress the immune system. Indeed, some of the agents recited in the specification, such as corticosteroids, cyclosporin, and FK506 (*see* page 6, lines 24-25), have been used for years as a therapeutic treatment for suppressing immunological rejection after organ transplant. The use and effectiveness of the immunosuppressive agent recited in the claims is well known in the art.

In Paper No. 13, the PTO cites a Linsley *et al.* document to question whether a certain immunosuppressive agent, CTLA4Ig, can lead to tolerance of two well-known and potent immunogens (SRBCs and KLH). The document, however, provides no logical barrier for the selection of an immunosuppressive agent in the claims at issue. As Paper No. 13 (page 4) indicates, "CTLA4Ig treatment induces long-term survival of pancreatic islet cell xenogrpahs." Applicants enclose a copy of the Lenschow *et al.* document referred to in Linsley (form PTO 1449 provided) and specifically note page 790, where the authors determined that CTLA4Ig treatment results in animals with 100% of the islet cell function, with no signs of rejection crisis. One skilled in the art would clearly recognize that data concerning xenogeneic cells is a superior example for the present situation than the extremely potent antigens (SRBCs and KLH) used in Linsley. Linsley's own statement, reiterated in Paper No. 13, that the potent immunogens they studied may confound the applicability of their results supports the conclusion that one skilled in the art would not find the data helpful to the situation here. Accordingly, when the appropriate information from Linsley is considered, one skilled in the art would logically conclude that the immune response to cells, such as those infected with a recombinant adenovirus, is effectively blocked or modulated by the one immunosuppressive agent discussed in Linsley.

Furthermore, the second document cited in Paper No. 13, Kay *et al.*, demonstrates that immunosuppressive agents, such as CTLA4Ig, do indeed prolong the expression of genes from adenoviral vectors. Page 191 and Figure 1 of that document show that animals that did not receive the immunosuppressive treatment had a 100-fold lower level of gene expression than those that did. The expression persists through at least the last data point, 160 days. This is direct evidence that immunosuppressive agents can be selected and used as the specification discloses they can be. In fact, Paper No. 13 does not discuss any other immunosuppressive agent other than CTLA4Ig or even why any other immunosuppressive agent does not work in the inventive compositions and methods. There is, therefore, no reason to question applicants' statements in the specification asserting that an immunosuppressive agent can be selected and used in the compositions and methods claimed (*see* page 10, lines 7-10).

With respect to the selection and use of an immunoprotective gene as recited in the claims, applicants also respectfully submit that no reason to question the enablement of the specification exists. Paper No. 13 points to the Kay *et al.* document as evidence that the use of recombinant adenoviruses is limited by the duration of gene expression from them (*see* page 4 of Paper No. 13). This document, however, merely points out the same issue that applicants note in the specification (*see* page 2, lines 24-28). This is an aspect that the current invention addresses by providing prolonged expression of the gene contained in the adenoviral vector (*see* the data in Example 2.3, for example).

Furthermore, the enclosed Poller *et al.* document confirms the applicability of this approach using the E3 region genes of adenovirus as an immunoprotective gene. "Our results obtained with an E3-[containing] vector for human factor IX [expression] indicate that the immunomodulating functions of the E3 region of wild-type adenovirus can be exploited to

stabilize transgene expression from E1-deleted replication-deficient adenoviral vectors" (*see* page 525 of Poller *et al.*). This confirms the statements in the specification that the combined use of an immunoprotective gene prolongs expression from the recombinant adenoviruses recited in the claims (*see* page 8, lines 6-12; and page 12, line 23 through page 13, line 5).

In contrast, the PTO provides no reasons to limit the applicability of the statements in the specification to only the exemplified immunosuppressive agents and immunoprotective genes as is done in Paper No. 13. In effect, Paper No. 13 concludes that the specification does not enable the claims because only certain examples of how to make and use the claims are actually in the specification. As noted above, the Examples should be taken to add to the understanding of one skilled in the art and not limit that understanding. Under this appropriate standard, the specification does indeed enable the pending claims.

Paper No. 13 asserts that "the effectiveness to create a permissive immune environment and to induce a state of tolerance with regard to predefined foreign antigens depends on the potency of the antigen, the immunosuppressive agent, and the immunoprotective gene used." (*See* page 5 of Paper No. 13.) Applicants do not understand what relevance the "effectiveness" characterization may have here. Applicants have shown in their specification, and have supplied independent evidence, that the recombinant adenoviruses recited do work in the methods and compositions claimed. Applicants have also shown that the Linsley *et al.* and Kay *et al.* documents (the only objective evidence provided in Paper No. 13) actually support the statements in the specification. These documents do not make applicants' statements unbelievable. It is the PTO's burden to establish that applicants' presumably enabling disclosure fails to teach how to make and use the invention. In re Brana, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995); In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1973). That has not been done here.

Furthermore, it is not applicants' burden to establish a clinically "effective" composition or method as required under the rules for Food and Drug Administration approval. The standard for § 112, first paragraph, falls well short of a demonstration of the therapeutic effectiveness that the FDA requires. *In re Brana*, 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995). Any desirable property, even if further research and development may be required, suffices. Here, at least the clearly desirable property of prolonging expression of the gene introduced by the recombinant adenovirus satisfies that burden. Thus, no further demonstration of "effectiveness" can be required.

Finally, Paper No. 13 states that the specification does not provide adequate guidance to enable the claims (*see* page 5). If the basis for this statement is the same used in support of the arguments citing the Linsley *et al.* and Kay *et al.* documents, applicants have already shown the error in this statement through the analysis above. If the basis for this statement is the quantity of experimentation, applicants have provided additional evidence that the claims are indeed enabled (Poller *et al.*). Furthermore, applicants submit that the examples in the specification should appropriately be considered for what they show and not what they do not show. Here, the examples show that modifying the immune system through an immunosuppressive agent and a immunoprotective gene allows prolonged expression from a recombinant adenoviral vector. That one skilled in the art is aware of additional immunosuppressive agents and additional immunoprotective genes cannot, by itself, show that the specification does not enable the claims or that one skilled in the art would doubt the statements in the specification supporting the claims. Indeed, the statements showing how the immunosuppressive agent operates (*see* page 9, lines 19-22, for example) in combination with the immunoprotective gene (*see* page 12, line 23 through page 13, line 5) to prolong expression

have been confirmed in Poller's published document. Nothing the PTO has cited as evidence detracts from the specification's enabling disclosure.

For these reasons, applicants respectfully submit that this rejection is in error and request its withdrawal.

Conclusion

Applicants believe that this application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with Applicants' representatives, in person or by telephone, we would welcome the opportunity to do so.

Respectfully submitted,
BAKER BOTTS L.L.P.

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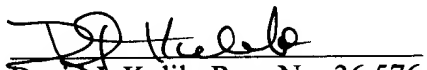
By: 
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